

**EXHIBIT II**  
**IND SUBMISSION**

February 28, 1997

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II  
Central Document Room  
12229 Wilkins Avenue  
Rockville, Maryland 20852  
Attn: Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products

**SCH 58235**  
**Capsules**  
**Serial No.: 000**

**SUBJECT: INVESTIGATIONAL NEW DRUG APPLICATION**

Dear Dr. Sobel:

Enclosed herein is an Investigational New Drug Application for SCH 58235 Capsules.

SCH 58235 is an azetidinone inhibitor of intestinal absorption of cholesterol that is being studied for treatment of primary hypercholesterolemia. The drug is structurally related to SCH 48461, for which relevant activity has been previously shown (IND 42075) but is more potent and thus far, has a safe profile in nonclinical studies, in doses smaller than SCH 48461. No unwanted pharmacologic effect has yet been observed nor has any particular target organ of toxicity been identified.

The first two clinical trials with SCH 58235 - randomized, double-blind studies of tolerability and pharmacokinetics associated with single or multiple doses taken orally following an overnight fast - have recently completed. Preliminary safety results from both studies and a preliminary evaluation of pharmacokinetics from the single-dose study are presented in section nine of this submission.

Based on preclinical safety studies the preliminary results of the rising single and rising multiple dose safety tolerability and pharmacokinetics, the sponsor is opening the IND with a Pilot Dose Ranging Study of the Safety and Efficacy of SCH 58235 Compared to Placebo and Lovastatin in Patients with Primary Hypercholesterolemia.

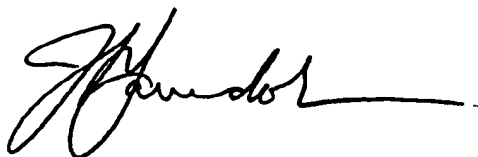
Center for Drug Evaluation and Research  
SCH 58235 Capsules

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Should you have any questions concerning this submission, please contact Ms. Mary Jane Boyle at (908) 298-5693.

Please be advised that material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

A handwritten signature in dark ink, appearing to read "J. Lamendola", followed by a horizontal line.

Joseph F. Lamendola, Ph.D.  
Vice President  
U.S. Regulatory Affairs

MJB/pjm  
Enclosures

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION**

**INVESTIGATIONAL NEW DRUG APPLICATION (IND)  
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)**

Form Approved: OMB No. 0910-0014  
Expiration Date: November 30, 1995.  
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

**1. NAME OF SPONSOR**

Schering Corporation

**2. DATE OF SUBMISSION**

February 28, 1997

**3. ADDRESS (Number, Street, City, State and Zip Code)**

2000 Galloping Hill Road  
Kenilworth, New Jersey 07033

**4. TELEPHONE NUMBER  
(Include Area Code)**

(908) 298-2628

**5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)**

SCH 58235 CAPSULES

**6. IND NUMBER (If previously assigned)**

**7. INDICATION(S) (Covered by this submission)**

Hypercholesterolemia

**8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED** ☐ PHASE 1 ☒ PHASE 2 ☐ PHASE 3 ☐ OTHER \_\_\_\_\_

(Specify)

**9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION**

None

**10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.**

SERIAL NUMBER:

0 0 0

**11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)**

☒ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

☐ RESPONSE TO CLINICAL HOLD

**PROTOCOL AMENDMENT(S):**

**INFORMATION AMENDMENT(S):**

**IND SAFETY REPORT(S):**

☐ NEW PROTOCOL

☐ CHEMISTRY / MICROBIOLOGY

☐ INITIAL WRITTEN REPORT

☐ CHANGE IN PROTOCOL

☐ PHARMACOLOGY / TOXICOLOGY

☐ FOLLOW-UP TO A WRITTEN REPORT

☐ NEW INVESTIGATOR

☐ CLINICAL

☐ RESPONSE TO FDA REQUEST FOR INFORMATION

☐ ANNUAL REPORT

☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED. ☐ OTHER \_\_\_\_\_

(Specify)

**CHECK ONLY IF APPLICABLE**

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR IND CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND (21 CFR 312.40) ☐ TREATMENT PROTOCOL (21 CFR 312.41) ☐ CHANGE REQUEST INDICATION (21 CFR 312.42)

**FOR FDA USE ONLY**

CDR/DBIND/OGD RECEIPT STAMP

DDR RECEIPT STAMP

IND NUMBER ASSIGNED:

DIVISION ASSIGNMENT:

## CONTENTS OF APPLICATION

This application contains the following items: (check all that apply)

- ☒ 1. Form FDA 1571 [21 CFR 312.23 (a) (1)]
- ☒ 2. Table of contents [21 CFR 312.23 (a) (2)]
- ☒ 3. Introductory statement [21 CFR 312.23 (a) (3)]
- ☒ 4. General investigational plan [21 CFR 312.23 (a) (3)]
- ☒ 5. Investigator's brochure [21 CFR 312.23 (a) (5)]
- ☒ 6. Protocol(s) [21 CFR 312.23 (a) (6)]
  - ☒ a. Study protocol(s) [21 CFR 312.23 (a) (6)]
  - ☐ b. Investigator data [21 CFR 312.23 (a) (6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ c. Facilities data [21 CFR 312.23 (a)(6)(iii)(b)] or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data [21 CFR 312.23 (a) (6)(iii)(b)] or completed Form(s) FDA 1572
- ☒ 7. Chemistry, manufacturing, and control data [21 CFR 312.23 (a) (7)]
  - ☒ Environmental assessment or claim for exclusion [21 CFR 312.23 (a) (7)(iv)(e)]
- ☒ 8. Pharmacology and toxicology data [21 CFR 312.23 (a) (8)]
- ☒ 9. Previous human experience [21 CFR 312.23 (a) (9)]
- ☐ 10. Additional information [21 CFR 312.23 (a) (10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO  
IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO  
IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS  
Cynthia Cuffie, M.D.  
Distinguished Clinical Research Physician  
Cardiovascular, Dermatology, Endocrinology

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG  
Robert J. Spiegel, M.D.  
Senior Vice President  
Worldwide Clinical Research

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE  
Joseph F. Lamendola, Ph.D.  
Vice President, U.S. Regulatory Affairs

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE



18. ADDRESS (Number, Street, City, State and Zip Code)  
2000 Galloping Hill Road  
Kenilworth, New Jersey 07033

19. TELEPHONE NUMBER  
(Include Area Code)  
(908) 298-2628

20. DATE  
2/28/97

(WARNING: A willfully false statement is a criminal offense U S C Title 18, Sec. 1001)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS  
Hubert H. Humphrey Building, Room 721-B  
200 Independence Avenue, S.W.  
Washington, DC 20201  
Attn: PRA

and to:

Office of Management and Budget  
Paperwork Reduction Project (0910-0014)  
Washington, DC 20503

Please DO NOT RETURN this application to either of the